

## PENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>0098125-VEmi</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 99/ 02001</b>	International filing date (day/month/year) <b>24/03/1999</b>	(Earliest) Priority Date (day/month/year) <b>29/03/1998</b>
Applicant <b>MERCK PATENT GMBH et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

USE OF ROR RECEPTORS FOR SCREENING SUBSTANCES USEFUL FOR THE TREATMENT OF  
ATHEROSCLEROSIS

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/02001

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
  
Y
2.  Claims Nos.: 14-16 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The description as well as claims 14-16 do not comply with the prescribed requirements to the extent that a meaningful search for these claims is not possible. The description does not sufficiently disclose the inventions of claim 14-16 (i.e. the substances selected by the screening method) by technical features of the substances themselves so as to allow the formulation of a meaningful search. In consequence the search for the second medical indication cannot be effected.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 14-16

The description as well as claims 14-16 do not comply with the prescribed requirements to the extent that a meaningful search for these claims is not possible. The description does not sufficiently disclose the inventions of claim 14-16 (i.e. the substances selected by the screening method) by technical features of the substances themselves so as to allow the formulation of a meaningful search. In consequence the search for the second medical indication cannot be effected.

## INTERNATIONAL SEARCH REPORT

International Application No

/EP 99/02001

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 721 096 A (KARATHANASIS SOTIRIOS K ET AL) 24 February 1998 see the whole document ---	1-11, 13, 17
X	LAVRENTIADOU, SOPHIA (1) ET AL: "Modulation of the ApoCIII promoter activity by heterodimers of ligand dependent nuclear receptors RXR -alpha-RAR -alpha, RXR -alpha-T3R-beta and RXR -alpha-PPAR-alpha." CIRCULATION, (1995) VOL. 92, NO. 8 SUPPL., PP. I291. MEETING INFO.: 68TH SCIENTIFIC SESSION OF THE AMERICAN HEART ASSOCIATION ANAHEIM, CALIFORNIA, USA NOVEMBER 13-16, 1995 ISSN: 0009-7322., XP002088668 *Abrégé: dernière ligne* --- -/-	1-13, 17

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

14 June 1999

Date of mailing of the international search report

21/06/1999

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

/EP 99/02001

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	VU-DAC, NGOC ET AL: "Retinoids increase human Apo C-III expression at the transcriptional level via the retinoid X receptor: contribution to the hypertriglyceridemic action of retinoids" J. CLIN. INVEST. (1998), 102(3), 625-632 CODEN: JCINA0; ISSN: 0021-9738, XP002088669 ---	1-13,17
A	JANUZZI, JAMES L. ET AL: "Characterization of the mouse apolipoprotein Apoa-1/ApoC-3 gene locus: Genomic, mRNA, and protein sequences with comparisons to other species" GENOMICS (1992), 14(4), 1081-8 CODEN: GNMCEP; ISSN: 0888-7543, XP002088670 see the whole document ---	1-13,17
A	OGAMI, K. ET AL.: "Promoter elements and factors required for hepatic and intestinal transcription of the human apoCIII gene" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 17, 1990, pages 9808-9815, XP002088671 cited in the application see figure 3 ---	1-13,17
A	TAYLOR, D.G. ET AL.: "Characterisation of a dominant negative mutant form of the NHF-4 orphan receptor." NUCLEIC ACIDS RESEARCH, vol. 24, no. 15, 1996, pages 2930-2935, XP002088672 see the whole document ---	1-13,17
A	JUMP D B ET AL: "Dietary fat, genes, and human health." ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1997) 422 167-76. REF: 70 JOURNAL CODE: 2LU. ISSN: 0065-2598., XP002088673 United States see the whole document -----	1-13,17

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

/EP 99/02001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5721096	A 24-02-1998	NONE	

REC'D 28 JUN 2000

WIPO

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference  0098125-VEmi	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No.  PCT/EP99/02001	International filing date (day/month/year)  24/03/1999	Priority date (day/month/year)  29/03/1998
International Patent Classification (IPC) or national classification and IPC  G01N33/50		
<p><b>Applicant</b>  MERCK PATENT GMBH et al.</p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I    <input checked="" type="checkbox"/> Basis of the report</li> <li>II   <input type="checkbox"/> Priority</li> <li>III   <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV   <input type="checkbox"/> Lack of unity of invention</li> <li>V   <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI   <input type="checkbox"/> Certain documents cited</li> <li>VII   <input type="checkbox"/> Certain defects in the international application</li> <li>VIII   <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>		

Date of submission of the demand  05/10/1999	Date of completion of this report  23.06.2000
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Stricker, J-E  Telephone No. +49 89 2399 8395



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/02001

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-46,52-54                  as originally filed

**Claims, No.:**

1-17                  as originally filed

**Drawings, sheets:**

1/17-17/17                  as originally filed

2. The amendments have resulted in the cancellation of:

the description,        pages:  
 the claims,              Nos.:  
 the drawings,            sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.  
 claims Nos. 14, 15, 16.

because:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/02001

the said international application, or the said claims Nos. 15 and 16, as regards industrial applicability, relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. 14.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 1-13, 15-17
	No:	Claims -
Inventive step (IS)	Yes:	Claims -
	No:	Claims 1-13, 15-17
Industrial applicability (IA)	Yes:	Claims 1-13, 15, 16
	No:	Claims -

**2. Citations and explanations**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/02001

**Section III**

**Claims 15 and 16** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1 (i) and (v) PCT. Consequently, no preliminary examination will be done with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Section V**

The first document cited as [X] in the ISR discloses the regulation of apoA-I by ARP-1 and RXR $\alpha$  which are different from ROR. The second document cited as [X] in the ISR teaches that the apoC-III promoter contains a HRE which is recognized by HNF-4, the latter being an orphan nuclear receptor but different from ROR. These documents are therefore not considered to be of particular relevance.

The following documents (D) have been cited by the applicant in the description; the numbering will be adhered to in the rest of the procedure:

D1: WO-A-95 27202 (cited on p.2, I.12)

D2: VU-DAC, NGOC et Al: "Transcriptional Regulation of Apolipoprotein A-I Gene Expression by the Nuclear Receptor ROR $\alpha$ ", J. Biological Chemistry (1997), 272(36), p.22401-22404 (cited as Ref.53 on p.2, I.29).

1. Document D1, which is considered to represent the most relevant state of the art, discloses (cf. abstract and the claims) a screening method from which the subject-matter of claims 1, 3 and 16 differs in that the selected substances have antiatherosclerotic properties / are useful in the treatment of lipid metabolism dysfunctions.

The subject-matter of **claims 1, 3 and 16** is therefore novel (Art. 33(2) PCT).

The problem to be solved by the present invention may therefore be regarded as to identify other metabolic pathways that are regulated by a ROR, that is, other genes whose expression can be modulated by a ROR, i.e. genes whose promoter

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/02001

contains a ROR responsive element (RORE).

The solution proposed in claims 1, 3 and 16 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

D2 discloses (cf. abstract) that ROR $\alpha$ 1 is an activator of apoA-I gene which contains a RORE (in the rat and mouse promoter). Since HDL and its major apolipoprotein apoA-I confer protection against atherosclerosis, the skilled person would have been sufficiently motivated to use the screening method of D1 in order to first identify substances having antiatherosclerotic properties / which are useful in the treatment of lipid metabolism dysfunctions, and second prepare a pharmaceutical composition useful for the treatment and/or prevention of atherosclerosis in humans or animals. Thus, the subject-matter of **claims 1, 3 and 16** does not involve an inventive step (Art. 33(3) PCT).

2. Dependent **claims 2 and 4-13** do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, the reasons being as follows:
  - a) **Claims 4-11** relate to vector constructions and to the use of compounds which are common in the art (cf. e.g. D1). ROR $\alpha$  (**claims 2 and 13**) is disclosed in D1 and D2.
  - b) Having selected a substance by the screening method of claim 3 (cf. item 1 above), the skilled person would have been sufficiently motivated to determine the effect of the said substance on the expression of apo C-III because it was known that apo C-III (cf. item 3 below) and apoA-I have adverse effects. Thus, the subject-matter of **claim 12** does not involve an inventive step (Art. 33(3) PCT).

Only a screening method wherein the effect on the expression of apo C-III is determined by using ROR receptors and/or their response element would appear to meet the requirements of Art. 33(3) PCT because it was not known that RORs are involved in the regulation of the expression of the apoC-III gene.

3. The subject-matter of **claim 15** is not disclosed in the known prior art and therefore would appear to be novel (Art. 33(2) PCT). Nevertheless, as disclosed in the present application (cf. p.3, l.15 to p.4, l.39), the role of apoC- III in hypertriglyceridemia, which leads to atherosclerosis, is well known in the art. Thus, the skilled person would regard it a normal design procedure to combine all the features set out in claim 15. The subject-matter of the said claim does therefore not involve an inventive step (Art. 33(3) PCT).
4. Since the method of claims 3-13 is novel, the subject-matter of **claim 17** can be considered as being novel as well (Art. 33(2) PCT. However, the said subject-matter would not appear to meet the requirements of Art. 33(3) PCT for the same reasons as those set out in item 2.b) above.

## **Section VIII**

1. **Claims 6 and 7** are not clear (Art. 6 PCT) for the following reasons:
  - a) "the toxic prodrug" in claim 6 lacks an antecedent
  - b) an inconsistency exists between the description and claim 6 as regards the gene whose expression is controlled ("suicide gene for selection" on p.10, l.1 and "selectable gene" in step a) of claim 6).
  - c) step b) in claim 7 and the description on p.10, l.26 should apparently read "another plasmid is created..."
2. Substances selected by a method of screening according to the present application (cf. p.11, l.39) do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT). One should bear in mind that no search was established for such selected substances.